REMARKS

Claims 1-31, 37-39 and 41-46 were pending in this application. Claims 3, 25, 27, 39, 41, 45 and 46 have been withdrawn by the Examiner as being drawn to non-elected inventions. Applicants acknowledge with thanks the rejoinder of claim 1 by the Examiner because claim 1, reciting "an artery," is generic to claim 2, which has been elected by Applicants and which recites "femoral artery." Claims 1-31, 37-39 and 41-46 remain pending in this application.

THE CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Applicants acknowledge with thanks that the previous rejection of claims 2, 4, 5, 7, 14, 15, 21, 22, 26, 28, 29, 31, 37 and 38 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,437,292 to Kipshidze *et al.* ("Kipshidze") has been withdrawn in response to arguments made by Applicants in the Amendment filed on January 16, 2009. However, claims 1, 2, 4, 5, 7, 14, 15, 21, 22, 26, 28, 29, 31, 37, 38, 43 and 44 are now rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 5,437,292 to Kipshidze *et al.* ("Kipshidze"). Claims 6, 19, 20, 23 and 42 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Kipshidze in view of U.S. Patent No. 6,162,241 to Coury *et al.* ("Coury"). Claims 8-13, 16-18, 24 and 30 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Kipshidze in view of U.S. Patent Application Publication No. 2002/0197302 to Cochrum *et al.* ("Cochrum"). Applicants respectfully disagree with these rejections for the reasons set forth below.

A. Claims 1, 2, 4, 5, 7, 14, 15, 21, 22, 26, 28, 29, 31, 37, 38, 43 and 44 Are Patentable Over Kipshidze

The Office Action states that the difference between Kipshidze and claims 1 and 2 is the provision that the composition is applied on the skin of a patient in need of such treatment (*see* Office Action at p. 4), thus acknowledging that Kipshidze does not disclose this element of the Applicants' claims. However, the Office Action further contends that it would have been obvious to one of ordinary skill in the art to provide the composition of Kipshidze to the compress that Kipshidze discloses to be used on the outer surface of the skin because the use of hemostatic patches (*i.e.*, a compress including a hemostatic composition, such as that disclosed

by Kipshidze, that is applied to the skin of a patient in need of such treatment) is well known in the art as allegedly acknowledged by Applicants in paragraph [0005] of the instant specification. Applicants respectfully disagree. Applicants submit that, on the contrary, paragraph [0005] confirms that, prior to the Applicants' invention, one of ordinary skill in the art would not have applied a hemostatic composition, such as that disclosed in Kipshidze, to the skin of a patient in the context of a cardiac catheterization procedure. Applicants further submit that it would not have been obvious to use the composition of Kipshidze on the outer surface of the skin in the context of a cardiac catheterization procedure for the reasons presented below.

(1) Paragraph [0005] of the Specification Does Not Acknowledge That Use of Hemostatic Compositions on the Skin During a Cardiac Catheterization Procedure Was Well Known in the Art

Paragraph [0005] discloses that hemostatic patches have been invented to treat *superficial wounds* on the skin or on the surface of internal organs, which are *effective at the site where the patch contacts the skin or the surface of an internal organ*. Paragraph [0005] describes the patches that were known in the art at the time of the Applicant's invention. Specifically, paragraph [0005] briefly describes compositions disclosed in U.S. Patents Nos. 6,056,970 to Greenawalt *et al.* ("Greenawalt"); 6,361,551 to Torgerson *et al.* ("Torgerson"); and 5,645,849[1] to Pruss *et al.* ("Pruss"). Paragraph [0005] further advises against use of such compositions during cardiac catheterization procedures. It states that application of known patches *in treatment of cardiac catheterization presents a problem* because the underlying puncture in the artery or vein is not directly affected by the active components of known patches, which may *lead to prolonged bleeding and the possibility of hematoma formation and other vascular complications*. Paragraph [0005] underscores the problem – inadequacy of known hemostatic patches to treat cardiac catheterization punctures at a distance from the site of application of the patch. None of references cited in paragraph [0005], *i.e.*, Greenawalt, Torgerson and Pruss, teach or suggest application of a composition that acts at a distance, such as a vasoconstrictor, to the skin of a patient in the context of a cardiac catheterization procedure.

[1] Paragraph [0005] of the specification erroneously cites U.S. Patent No. 5,**564**,849 instead of 5,**645**,849. This is an inadvertent typographical error. The erroneously cited patent is directed to curved writing instruments and not to hemostatic patches described in [0005].

Greenawalt discloses hemostatic compositions that induce blood clotting when a composition is "*maintained in contact with the wound*...for a period of time sufficient for blood clotting to occur *at the interface between the composition and the wound*..." *See* col. 6, lines 3-7 (emphasis added). Nothing in Greenawalt suggests that such blood-clotting composition may work when applied at a distance from the wound, and nowhere does Greenawalt suggest such application of its composition. In fact, in the context of vascular procedures, Greenawalt does not teach application of its hemostatic composition to the skin. Instead, Greenawalt discloses that a hemostatic composition can be provided "for use to anastomose or fuse ends of a blood vessel" "to fit the ends of the vascular prosthesis." *See* col. 6, lines 28-40; and claim 21 at col. 16, lines 28-29. Example 11 of Greenawalt further describes how, in the vena cava puncture model, the test hemostatic article was placed over the wound in vena cava and "then *removed from the vena cava in one piece using forceps*." *See* Example 11 at col. 12, lines 51-63 (emphasis added). Greenawalt clearly suggests that, in the contexts of vascular procedures, the hemostatic test article should be applied directly to the puncture, not to the skin at a distance from a puncture. Thus, in the context of vascular procedures, where the wound is removed from the skin, Greenawalt does not teach or suggest application of a hemostatic composition to the skin of a patient. In addition, nowhere does Greenawalt teach or suggest use of a vasoconstrictor or any composition that may work at a distance from its application, much less use of a vasoconstrictor on the skin in the context of a cardiac catheterization procedure as recited in the Applicant's claims.

As Greenawalt, Torgerson and Pruss describe hemostatic compositions or fabrics that work by promoting blood clotting when "the fabric is maintained in contact with the surface for a period of time sufficient for clotting to occur at the interface between the hemostatic fabric of the invention and the surface." *See* Torgerson at col. 2, lines 42-47; and col. 10, lines 61-64; and Pruss at col. 3, lines 1-5; and col. 6, lines 38-45. Nothing in Torgerson or Pruss suggest that such blood-clotting composition may work at a distance. Furthermore, both Torgerson and Pruss specifically distinguish between topical applications of its hemostatic fabrics (such as for burn and tissue transplants) and internal-surgical applications (such as for vascular surgery). *See* Torgerson at col. 11, lines 26-28, 32-24, 63-64; and col. 12, lines 8-11; and Pruss at col. 7, line 61 to col. 8, line 10. For internal-surgical applications, both Torgerson and Pruss specifically

teach that the layer(s) of the fabric must be "both biodegradable and pharmaceutically acceptable," because the application is internal not topical, *i.e.*, not on the skin. *See* Torgerson at col. 12, lines 8-11; and Pruss at col. 7, lines 23-25 and col. 8, lines 7-9. In the context of vascular procedures, both Torgerson and Pruss teach use of its patch to anastomose or fuse ends of a blood vessel by wrapping the patch around the external surface of the ends of a graft. *See* Torgerson at col. 11, line 28 and col. 12, lines 12-26; and Pruss at col. 8, lines 11-18. Neither Torgerson nor Pruss teach or suggest application of any composition to the skin of a patient, at a distance from a wound, in the context of a vascular procedure such as a cardiac catheterization procedure. In addition, Torgerson does not teach or suggest use of any vasoconstrictor; whereas Pruss only discloses use of a vasoconstrictor, *i.e.*, epinephrine, *by injection* in order to raise arterial pressure in animal models to study effects of its test articles. *See* Pruss at col. 15, lines 20-21. Neither Torgerson nor Pruss teach or suggest use of any composition that may work at a distance from its application, such as a vasoconstrictor, on the skin in the context of a cardiac catheterization procedure.

To summarize, paragraph [0005] and references cited therein suggest that in the context of vascular procedures topical, on the skin, application of a hemostatic composition was not known or practiced. Further, paragraph [0005] and references cited therein do not teach or suggest use of any composition that may work at a distance from the site of application, such as a vasoconstrictor. Furthermore, paragraph [0005] warns against application of previously known hemostatic patches to the skin during a cardiac catheterization procedure because such compositions are effective only at the site of contact and their administration may cause vascular complications. Paragraph [0006] confirms this stating that "[s]ince [the known compositions] are effective at the site of contact, topical treatment [of] a breach or puncture in a vein or artery that is found at some distance from the skin surface is not possible," and thus "it is necessary to apply the compositions in an invasive manner."

(2) It would not have been Obvious to Use the Composition of Kipshidze on the Outer Surface of the Skin in the Context of a Cardiac Catheterization Procedure

As explained in the Amendment filed on January 16, 2009 (*see* pp. 10 and 12), Kipshidze does not teach or suggest any non-invasive means for applying its hemostatic composition.

Instead, Kipshidze states that it is an object of its invention to provide an invasive method for applying a fibrin sealant, *i.e.*, directly to the external wall of an arterial or venous puncture site (*see* col. 2, lines 14-16), in order to form a seal or clot around the puncture which will prevent blood leakage from the vessel into the surrounding tissue (*see* col. 6, lines 22-26). By teaching application of its composition directly to the external wall of the puncture site to seal the puncture, Kipshidze leads away from the indirect, at a distance, application claimed by Applicants. In considering a prior art reference, the reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *See W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984); and M.P.E.P. § 2141.03.VI (8th ed. Rev. July 2008).

Further, contrary to the contention in the Office Action (*see* p. 4), it would not have been obvious to one of ordinary skill in the art to use the composition of Kipshidze on the outer surface of the skin because the fibrin sealant composition of Kipshidze simply does not work at a distance from its application. The hemostatic compositions comprising fibrin, such as the composition of Kipshidze, are effective at the site of contact, not at a distance. *See* specification at [0006]. "In order to treat breaches or punctures in veins or arteries at a distance beneath the skin surface with such compositions, it is necessary to apply the compositions in an invasive manner." *See* specification at [0006]. One of ordinary skill in the art would know that the fibrin sealant of Kipshidze does not work at a distance, and thus would not apply the composition of Kipshidze on the skin at a distance from the vascular puncture.

Moreover, the purpose of the composition of Kipshidze is to form a seal in an artery a vein, which is only possible if the sealant is applied under the skin, directly to the vicinity of the puncture site. Application of the composition of Kipshidze on the skin would render the composition and methods of Kipshidze unsatisfactory for their intended purpose. If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 U.S.P.Q. 1125 (Fed. Cir. 1984); *see* also M.P.E.P. § 2143.01.V (8th ed. Rev. July 2008).

For the reasons presented above, it would not have been obvious for one of ordinary skill in the art in view of Kipshidze and references cited in paragraph [0005] to apply a hemostatic

composition on the skin over a catheter exit site in the context of a cardiac catheterization procedure.

(3) The Claimed Invention Is Directed to a New Method of Treating Vascular Punctures Caused by Cardiac Catheterization By Application of a Vasoconstrictor on the Skin

Hemostatic patches that were known in the art before the Applicant's invention "are effective at the interface of the wound and the patch." *See* specification at [0007]; and disclosures of Greenawalt, Torgerson and Pruss. Paragraph [0007] of the specification describes the problem that application of such patch may cause when applied to the skin to treat a puncture in a vein or artery caused by catheterization – "when a patch causes clotting at the skin surface wound site, the deeper internal puncture in a vein or artery continues to hemorrhage increasing the likelihood that a hematoma or other vascular complications will occur." On the other hand, hemostatic compositions intended for percutaneous application, such as the composition of Kipshidze, are invasive and can lead to complications such as swelling, further damage to blood vessels and tissue, and increased risk of infection. *See* specification at [0006]. These are the problems to which the Applicant's claimed invention provided a solution.

It is the inventors of the claimed invention who were the first to conceive of the use of one or more vasoconstrictor on the skin over a catheter exit site, at a distance from a puncture in a vein or artery, in the context of a cardiac catheterization procedure. The specification as originally filed states that "the main feature of the methods and compositions of the invention over the existing hemostatic patches and devices is the non-invasive manner in which the compositions function and can be applied." *See* [0010], emphasis added. The invention is based upon the concept of treating a breach or puncture in a vein or artery from a distance via a skin surface wound contiguous with the breach or puncture. See specification at [0040]. The advantage of such non-invasive application of a composition, at a distance from vascular puncture, is decrease in likelihood of localized vascular complications associated with a cardiac catheterization procedure. *See* specification at [0010]. The claimed composition works when applied to the skin surface at a distance from the breached blood vessel of 1 cm or more. In fact, independent claims 1 and 2 specifically recite applying the claimed composition over a catheter exit site on the skin of a patient, wherein the catheter exit site is contiguous with the catheter

puncture by 1-10 cm. It would not have been obvious to one of ordinary skill in the art over Kipshidze and references cited in paragraph [0005] of the Applicants' specification to apply a hemostatic composition, specifically a vasoconstrictor, on the skin where the wound is removed from the skin by 1-10 cm. In fact, this was contrary to the understandings and expectations that existed in the art.

For at least the foregoing reasons, independent claims 1 and 2, and dependent claims 4, 5, 7, 14, 15, 21, 22, 26, 28, 29, 31, 37, 38, 43 and 44 are patentable over Kipshidze.

B. Claims 6, 19, 20, 23 and 42 Are Patentable Over Kipshidze In View Of Coury

Regarding the rejections of claims 6, 19, 20, 23 and 42 over Kipshidze in view of Coury, Applicants submit that these claims are not obvious over Kipshidze in view of Coury by virtue of their dependency from claims 1 or 2, which in turn are not obvious over these references for the following reasons.

As discussed above, Kipshidze does not make obvious application of a vasoconstrictor on the skin in the context of a cardiac catheterization procedure. Coury does not cure the deficiencies of Kipshidze. Like Kipshidze, Coury also does not teach or suggest applying its composition over a catheter exit site on the skin of a patient in the context of a cardiac catheterization procedure. Moreover, as described in detail in the Amendment filed by Applicants on January 16, 2009 (see pp. 12-13), one of ordinary skill in the art would have no reason to modify the composition of Kipshidze to include the additional elements disclosed in Coury, because Coury teaches away from using fibrin sealants such as those taught by Kipshidze (*see* Coury at col. 1, lines 24-30). It is improper to combine references where the references teach away from their combination. *See In re Grasselli,* 713 F.2d 731, 743 (Fed. Cir. 1983); and M.P.E.P. § 2145.X.D(2) (8th ed. Rev. July 2008).

For at least the foregoing reasons, independent claims 1 and 2, and dependent claims 6, 19, 20, 23 and 42 are patentable over Kipshidze in view of Coury.

C. Claims 8-13, 16-18, 24 and 30 Are Patentable Over Kipshidze In View Of Cochrum

Regarding the rejections of claims 8-13, 16-18, 24 and 30 over Kipshidze in view of Cochrum, Applicants submit that these claims are not obvious over Kipshidze in view of Cochrum by virtue of their dependency from claims 1 or 2, which in turn are not obvious over these references for the following reasons.

Cochrum does not cure the deficiencies of Kipshidze described in section A of this response. As described in detail in the Amendment filed by Applicants on January 16, 2010 (see p. 14), Cochrum also teaches only direct, percutaneous application of its compositions in the context of vascular procedures by teaching internal application of its compositions to plug an artery or vein (*see* Cochrum at page 16, paragraph [0229]; page 17, Example 5; and page 17-18, Example 8). Cochrum teaches topical application of its compositions to the skin only in the context of superficial wounds, *e.g.*, superficial cuts, abrasions, punctures, sores, and burn or tissue transplants (*see* paragraphs [0209], [216], and [218]). Therefore, not only does Cochrum fail to provide the teaching or suggestion missing from Kipshidze, Cochrum also teaches away from application of a hemostatic composition on the skin in the context of vascular procedures such as a cardiac catheterization procedure. *See W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984); and M.P.E.P. § 2141.03.VI (8th ed. Rev. July 2008).

Furthermore, as described in detail in the Amendment filed by Applicants on January 16, 2009 (see p. 14), one of ordinary skill in the art would have no reason to modify the composition of Kipshidze to include the additional elements disclosed in Cochrum, because Cochrum teaches away from using fibrin sealants such as those taught by Kipshidze (*see* Cochrum, page 3, paragraph [0037]-[0039]; and page 4, paragraphs [0049] to [0051]). *See In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983); and M.P.E.P. § 2145.X.D(2) (8th ed. Rev. July 2008).

For at least the foregoing reasons, independent claims 1 and 2, and dependent claims 8-13, 16-18, 24 and 30 are patentable over Kipshidze in view of Cochrum.

CONCLUSION

For at least the reasons given above, Applicant respectfully requests the Examiner to reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned attorney if a telephone call would help resolve any remaining issues.

Applicant respectfully requests that the foregoing remarks be entered and made of record in the file history of the above-identified application.

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